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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/621,448	07/21/2000	MICHAEL R. O'DONOHUE	1533.1010002/SRL/CMb	4431

7590

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EXAMINER

STEADMAN, DAVID J

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 01/25/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

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Advisory Action

Application No.

09/621,448

Applicant(s)

O'DONOHUE ET AL.

Examiner

David J. Steadman

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 December 2001 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) ☐ they raise the issue of new matter (see Note below);
 - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: NONE.Claim(s) objected to: NONE.Claim(s) rejected: 1,6-8 and 18-21.

Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☐ Other:

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ADVISORY ACTION

Claims 1, 6-8, and 18-21 are pending in the application.

Applicants' amendment to claims 1, 6, and 8 in Paper No. 12 is acknowledged.

Due to the numerous amendments to the claims, the examiner requests that applicants provide a copy of all pending claims in subsequent communications.

The request for reconsideration has been considered but does not place the case in condition for allowance for the reasons discussed below.

1. In view of applicants' amendment to claims 1, 6, and 8 to specifically identify the alteration of the *C. glutamicum* cell by reciting a *Corynebacterium glutamicum* cell with a disrupted *pgi* gene, the written description rejection under 35 U.S.C. 112, first paragraph, is withdrawn.

2. The written description rejection of claims 7 and 18-21 under 35 U.S.C. 112, first paragraph, is maintained. Applicants argue that claims 1, 6-8, and 18-21 have been amended to recite a method of producing the recited amino acids comprising culturing a *C. glutamicum* cell with a disrupted *pgi* gene. The examiner agrees that the amendment to claims 1, 6, and 8 to recite said method using a *C. glutamicum* cell with a disrupted *pgi* gene provides sufficient written description of the claimed invention to overcome the instant rejection. However, claims 7 and 18-21 *have not* been amended as stated by applicants (page 5 of Paper No. 12, lines 3-6) to include a *C. glutamicum* cell with a disrupted *pgi* gene. Therefore, rejection of claims 7 and 18-21 is maintained for the reasons of record (see Paper Nos. 9 and 11).

3. In view of applicants' amendment to claims 1 and 6 to specifically identify the alteration of the *C. glutamicum* cell by reciting a *Corynebacterium glutamicum* cell with a disrupted *pgi* gene, the enablement rejection under 35 U.S.C. 112, first paragraph, is withdrawn.

4. The enablement rejection of claims 7 and 18-20 under 35 U.S.C. 112, first paragraph, is maintained. Applicants argue that claim 1 has been amended such that the claim is directed to a method of producing the recited amino acids comprising culturing a *C. glutamicum* cell with a disrupted *pgi* gene. The examiner agrees that the amendment to claims 1 and 6 to recite said method using a *C. glutamicum*

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cell with a disrupted *pgi* gene provides sufficient enablement to overcome the instant rejection. However, claims 7 and 18-20 *have not* been amended as stated by applicants (page 5 of Paper No. 12, lines 3-6) to narrow the scope of the claim to a *C. glutamicum* cell with a disrupted *pgi* gene. Therefore, rejection of claims 7 and 18-20 is maintained for the reasons of record (see Paper Nos. 9 and 11).

5. Rejection of claims 1, 6, 7, and 18-20 under 35 U.S.C. 103(a) as being unpatentable over Mascarenhas et al. (Appl Environ Microbiol 57:2995-9) in view of Ishino et al. (J Gen Appl Microbiol 37:157-165), Voet et al. (Biochemistry 2nd Edition, Wiley and Sons, 1995, NY), and Sahm et al. (Ann NY Acad Sci 782:25-39), is maintained. Applicants argue that Mascarenhas et al. suggest only that the deletion of the *E. coli* *pgi* gene may have an effect on the biosynthetic capabilities of *E. coli* production of aromatic intermediates. The examiner disagrees. Mascarenhas et al. teach that deletion of *pgi* gene in *E. coli* diverts carbon flow from glycolytic pathways into the HMP shunt, thereby increasing production of NADPH resulting in increased production of tryptophan and glutamate (page 2998, right column).

Applicants argue that, contrary to the examiner's assertion of similarity of amino acid biosynthetic pathways in bacteria, Sahm et al. teach that amino acid biosynthetic pathways vary significantly among bacterial strains and therefore, one of ordinary skill in the art would not have a reasonable expectation of success for increasing production of the recited amino acids by disruption of the corresponding *pgi* gene in *C. glutamicum*. Applicants argue that Sahm et al. teach that *E. coli* and *C. glutamicum* utilize two *distinct* lysine biosynthetic pathways. Applicants' argument is not found persuasive. Sahm et al. teach (page 28) that all procaryotes including *E. coli* utilize one of three pathways for D,L-diaminopimelate and L-lysine synthesis, while *C. glutamicum* has the ability to use two pathways – an essential pathway which is identical to the pathway used by *E. coli* and a non-essential pathway. Inspection of the pathways as shown in Figure 3 demonstrates that the pathways *are not distinct* and are nearly identical, with differences only in the intermediates from the conversion of piperidine-2,6-dicarboxylate to D,L-diaminopimelate. Therefore, the non-essential pathway is identical to the essential pathway, except that the non-essential pathway bypasses 3 intermediates in the essential pathway and converges with the essential pathway at the D,L-diaminopimelate intermediate step (page 30, Figure 3). As stated in Paper

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Nos. 9 and 11, Mascarenhas et al. teach that deletion of *pgi* gene in *E. coli* diverts carbon flow from glycolytic pathways into the HMP shunt, thereby accelerating the generation of NADPH (with increased production of tryptophan and glutamate), Ishino et al. teach that increased carbon flow through the HMP shunt in *C. glutamicum* results in increased yields of L-lysine due to an increased production of NADPH, and Voet et al. teach that biosynthesis of the recited amino acids requires NADPH (pages 771-2). It is noted that the step at which NADPH is required in the biosynthesis of lysine (conversion of L-2,3-dihydrodipicolinate to L-delta'-piperidine-2,6-dicarboxylate, page 30, Figure 3 of Sahm et al. and page 771 of Voet et al.) does not involve intermediates that are by-passed in the non-essential pathway of L-lysine biosynthesis of *C. glutamicum*. Therefore, one of ordinary skill in the art would have a reasonable expectation of success for increased yields of L-lysine, L-threonine, and L-isoleucine by disruption of the *C. glutamicum pgi* gene.

Applicants argue the rejection is based on impermissible hindsight reasoning in concluding that the invention is obvious as there is no suggestion or motivation to combine that cited references, and even with a combination of the cited references, there would be no reasonable expectation of success and the prior art references do not teach or suggest all of the claim limitations. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicants also argue that the references of Mascarenhas et al., Ishino et al., Voet et al., and Sahm et al. individually or combined do not teach the claimed invention. The examiner disagrees. While the individually cited references do not teach the claimed invention, it is the combination of the references that teach the claimed invention, provide motivation for practicing the invention, and demonstrate an expectation of success for practicing the claimed invention.

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The rejection is maintained for the reasons discussed above and for the reasons of record presented in Paper Nos. 9 and 11.

6. Rejection of claims 8 and 21 under 35 U.S.C. 103(a) as being unpatentable over Mascarenhas et al. in view of Ishino et al., Voet et al., and Sahm et al. as applied to claims 1, 6, 7, and 18-20 and further in view of Fitzpatrick et al. (Appl Microbiol Biotechnol 42:575-580) is maintained. Applicants argue that Mascarenhas et al. discloses a *pgi*-null *E. coli* and not a *pgi*-null *C. glutamicum* and that Fitzpatrick teaches a method of gene silencing of the *recA* gene of *C. glutamicum* and therefore, the cited references do not combine for a prima facie case of obviousness over the claimed invention. Applicants reiterate the argument that, based on the teachings of Sahm et al., one of ordinary skill in the art would not have a reasonable expectation of success for increasing yields of the recited amino acids by disrupting the *pgi* gene in *C. glutamicum*. Applicants' argument is not found persuasive. As stated above, Sahm et al. do not teach distinct L-lysine pathways for *E. coli* and *C. glutamicum*, but that the L-lysine biosynthetic pathway for *E. coli* pathway the essential pathway for *C. glutamicum* are identical. As previously stated, while the individually cited references do not teach the claimed invention, it is the combination of the references that teach the claimed invention, provide motivation for practicing the invention, and demonstrate an expectation of success for practicing the claimed invention.

Therefore, the combination of the cited references would provide one of ordinary skill in the art a reasonable expectation of success for practicing the claimed methods of producing amino acids using a *C. glutamicum* with a disrupted *pgi* gene by applying the teachings of Fitzpatrick et al. in order to delete the *C. glutamicum* *pgi* gene by homologous recombination.

The rejection is maintained for the reasons discussed above and for the reasons of record presented in Paper Nos. 9 and 11.

7. No claim is in condition for allowance. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804.


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The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.


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1600